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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/970,045	11/13/1997	EUGEN KOREN	20487/113	2118

7590 12/05/2001

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	PAPER NUMBER
1645	25

DATE MAILED: 12/05/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/970,045	Kores
Examiner	**Group Art Unit**
Duffy	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 9-5-01.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-13, 39-47 is/are pending in the application.

Of the above claim(s)____ is/are withdrawn from consideration.

☒ Claim(s) 46-47 is/are allowed.

☒ Claim(s) 1-13, 39-45 is/are rejected.

☒ Claim(s) 3,5-45 is/are objected to.

☐ Claim(s)____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s).____

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other____

Office Acti n Summary

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 9-5-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/970,045 is acceptable and a CPA has been established. An action on the CPA follows.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. Any rejection not reiterated herein is withdrawn based on Applicants' amendments or for reasons set forth below.

The rejection of claim 46 under 35 U.S.C. 102(b) as being clearly anticipated by Curtiss et al (U.S. Patent 4,677,057, issued June 30, 1987) is withdrawn because Curtiss et al does not teach that the epitope is uninfluenced by the lipid content of the lipoprotein, apolipoprotein or lipid associated with a specific lipoprotein.

Priority

4. The status of nonprovisional parent application(s) (whether patented or abandoned) should be updated. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application.

Rejections Maintained

5. The rejection of claim 39 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record in Paper No. 12, mailed 6-27-00.

Applicants arguments have been carefully considered but are not persuasive. The specification is drawn to apolipoproteins and the claims are drawn to lipoproteins. Applicants mismatch lipoproteins and apolipoproteins. Lipoproteins

are an art recognized distinct entity as compared to apolipoproteins (Vance et al, Biochemistry of Lipids and Membranes, pages 426 and 427). Apolipoproteins are components of lipoproteins and the concept of the specification are for non-cross reactive antibodies are for apolipoproteins and not lipoproteins as asserted. Applicants apparently argue that they are synonymous, they are not.

6. The rejection of claims 42-45 under 35 U.S.C. 103(a) as being unpatentable over Koren et al (Atherosclerosis, 95:157-170, 1992)is withdrawn is maintained for reasons made of record in Paper No. 12, mailed 6-27-00.

Applicants argue that the antibody of Koren et al is not specific for HDL, LDL or VLDL and that does not teach that the epitope bound by any one of the monoclonal antibodies used in the paper is uninfluenced by the lipid content of the lipoprotein, apolipoprotein or lipid associated with a specific lipoprotein. It is noted that the claim does not require that the antibody be specific for a specific lipoprotein (i.e. that specifically binds apoB in HDL). As such, Applicants arguments are not persuasive.

7. The rejection of claims 1, 10 and 11 under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) in view of Koren et al (Atherosclerosis, 95:157-170, 1992) is maintained for reasons made of record in Paper No. 19, mailed 3-8-01.

Applicants arguments have been carefully considered but are not persuasive. Inasmuch as the rejections have been traversed together they have been rebutted together. Applicants argue that their is no disclosure of the using multiple antibodies immunoreactive with LDL, HDL or VLDL on the same substrate to provide a comparative ratio. This is not persuasive, the claim as written clearly specifies "or at least two different apolipoproteins". The rejection as combined provides for a ratio of ApoB and Apo AI on a solid phase, wherein one of the antibodies has the claimed characteristics because the ApoB antibodies of Koren et al bind all the indicated apolipoproteins present regardless of density class and therefore bind epitopes uninfluenced by lipid associated with lipoprotein. The

claims do not require that the antibodies also be specific for a lipoprotein as asserted. Lipoproteins and apolipoproteins are different entities. The examiner emphasizes that the recited antibodies in the claim do not have to be specific for a specific lipoprotein, they are alternatively immunoreactive with an apolipoprotein in the claims. Applicants also assert that the antibodies must be uninfluenced by a lipid associated with a lipoprotein. Koren et al teach that the pan anti-apolipoprotein antibodies bind all the apolipoprotein in serum regardless of the lipoprotein density class that it is associated with. As such, the antibodies of Koren et al teach antibodies that meet the limitation of "uninfluenced by lipid associated with the specific lipoprotein as is claimed. Applicants also argue that the Scripps teach that the lipid associated with the chylomicrons affecting binding to ApoB-100 at page 17, lines 10-20. Page 17, lines 10-20 do not indicate that lipid interferes with antibody binding but that the size of the chylomicrons prevents all apoB-100 from binding to the solid phase (i.e stearic interference, not masking of an epitope by lipid). The fact that the antibody reacted with three lipoproteins is irrelevant, since the claims do not require that the antibodies be specific for an apolipoprotein in a specific lipoprotein. Applicants also argue that Lucas teaches the desirability of removing other components because they have an effect on the assay. It is noted that the current claims have comprising language and therefore are open to washing and processing steps not specifically recited in the claims. Additionally, the type of immunogen used by Lucas is irrelevant to the claimed invention.

Applicants are directed to allowable subject matter below that reflects applicants arguments that the antibodies must be lipoprotein specific.

8. The rejection of claim 6 under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) and Koren et al (Atherosclerosis, 95:157-170, 1992) as applied to claims 1, 10 and 11 above, and further in view of Luca (EP 0 407 035, published 2/3/88 is maintained for reasons made of record.

9. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990), Koren et al (Atherosclerosis, 95:157-170, 1992) and Luca (EP 0 407 035, published 2/3/88) and as applied to claim 6 above, and further in view of Mills et al (Laboratory Techniques in biochemistry and molecular biology, Volume 14, A Guidebook to Lipoprotein Technique; 1984, pages 472-478) is maintained for reasons made of record.

10. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) and Koren et al (Atherosclerosis, 95:157-170, 1992) as applied to claims 1, 10, and 11 above, and further in view of Scripps Clinic (EP 0 257 778, published 2/3/88) is maintained for reasons made of record.

11. Claims 1, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990), Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990)and Koren et al (Atherosclerosis, 95:157-170, 1992) as applied to claims 1, 10 and 11 above, and further in view of Curtiss et al (U.S. Patent 4,677,057, published June 30, 1987) is maintained for reasons made of record.

New Rejections/Objections

Claim Objections

12. Claims 3, 5 and 45 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s)

to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, the independent claim is drawn to monoclonal antibodies and claim 3 fails to limit the monoclonal antibody used. Claims 3 and 45, broadens the scope of the independent claim by reciting recombinant antibodies or antibody fragments. Claim 5, broadens the scope of the claim by reciting a particular recombinant, rather than monoclonal antibody. See allowable subject matter below for guidance on alternative language.

13. Claims 1-13, 40-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims 1-11, the claims remain indefinite for the following reasons. It is still unclear that each of the first and second antibodies must bind different lipoproteins. Applicants amendment is insufficient to provide for the concept that each of the first and second antibody bind different lipoproteins. Applicants amendment merely require that they bind different epitopes and the epitopes can still be on the same lipoprotein. Applicants are again directed to the examiners suggested language. Second, the preamble no longer matches the steps and the final outcome of the method. The preamble is directed to determining the relative ration of at least two different apolipoproteins in a biological sample, but the base claim determines the amount of LDL, HDL or VLDL lipoprotein. How are the amount of the lipoproteins dispositive of a preamble directed toward a relative ratio of at least two different apolipoproteins. As to claim 6, the claim is confusing because a lipid stain does not detect lipoprotein but rather detect lipoprotein lipid. Amendment of the claim to recite "... determining the amount of lipoprotein lipid or lipid associating..." would obviate this rejection. As to claim 9, the claim is confusing because "the apolipoprotein" lacks clear antecedent basis. What apolipoprotein does this clearly reference ? Do they bind the same or different apolipoprotein. Since at least 2 are required by the preamble of the claims, it is unclear to which one or both Applicants are reference.

As to claim 12 and dependent claim 13, the claim recites an improper Markush group in the recitation of "lipid associated with a specific lipoprotein selected from the group consisting of different apolipoprotein in a conformation

and lipid independent manner". No Markush members are recited. Further, the claim fails to determine the concentration of at least two different apolipoproteins in a biological sample as set forth in the preamble. The method steps only achieve the determination of the apolipoprotein bound to either the first or second monoclonal antibody and the third immobilized monoclonal antibodies. As such, the goal of the preamble does not match the method steps and final outcome of the assay.

As to claim 40, the amendment to recite "... separating the complexed anti-ApoC-III antibody ApoC-III containing lipoprotein particles from the biological sample.." renders the claim unclear because now, it is unclear which how determining the amount of apoC-III present in HDL in the anti-Apo C-III-anti Apo A-I complexed material in the sample" is achieved.. The complex that is should be separated is the anti-Apo C-III-anti Apo A-I complexed material, otherwise the assay does not achieve the goal of the method steps. The claim lacks a step of determining the amount of the amount of Apo C-III present in the VLDL in the Pan B-anti-ApoC-III complexed material in the sample, as such the method is incomplete as written because a ratio of two points can not be derived from a point that has not been determined.
Correction is required.

As to claim 41, the claim is now indefinite because the antecedent basis for "the antibodies reactive with Apo E in the biological sample now falls to that defined in step (a) and by definition these monoclonal antibodies do not bind apoE associated with HDL (i.e. are specific for Apo E in VLDL). As such, it is not clear how any apoE present in HDL is detected or determined, when non antibodies that bind ApoE present in HDL are present in the assay.

As to claims 42 and 43, the claims are rendered indefinite because the Markush group in the later half of the claim recites ApoB however, the Apo B antibody of the claim is nota recited monoclonal or recombinant antibody and therefore lacks antecedent basis in the claim.

As to claims 44 and 45, the term "predominantly" is a relative term which renders the claim indefinite. The term "predominantly" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite

degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Allowable Subject Matter

Claim A. A method for determining the relative ratio of at least two different lipoproteins in a biological sample comprising:

immersing into the sample a solid phase material having separately immobilized thereon at least a first and second antibody wherein the first and second antibodies are selected from the group consisting of monoclonal antibodies, recombinant antibodies and antigen binding fragments thereof, wherein the first and second antibodies each specifically bind different lipoproteins selected from the group consisting of: LDL, HDL and VLDL, and wherein the first and second antibodies are immunoreactive with a stable, conformation independent epitope which is uninfluenced by the lipid content of a specific lipoprotein, apolipoprotein and lipid associated with a specific lipoprotein;

PAD 12/3/01

allowing the monoclonal antibody molecules time to bind the lipoproteins in the sample;

removing the solid phase material containing the immobilized antibodies molecules;

determining the amount of each different lipoprotein bound by the immobilized antibodies;

comparing the amount which is specific for each different lipoprotein in order to calculate the relative amount of two different lipoproteins.

The method of claim A, wherein the lipoproteins are HDL and LDL.

The method of claim A, wherein the first or second antibody is the anti-LDL monoclonal antibody produced by the hybridoma cell line HB_3cB_3 American Type Culture Collection Number HB 11612.

The method of claim A, wherein the first or second monoclonal antibody is recombinant anti-LDL $RcB_3M_1D_4$ American Type Culture Collection Number HB 69602.

The method of claim A, further comprising determining the amount of lipoprotein lipid by staining the material bound to the immobilized antibody using a lipid stain.

The method of claim (directly above), wherein the lipid stain is selected from the group consisting of Sudan Red 7B, Old Red O and Sudan Black B.

The method of claim (two above), wherein the lipoprotein lipid is stained prior to immersing the immobilized antibodies.

The method of claim A, further comprising measuring the amount of protein associated with the lipoproteins in the sample, further comprising the step of providing additional antibodies that specifically bind an apolipoprotein present in the selected lipoprotein, wherein the antibodies that specifically bind an apolipoprotein present in the selected lipoprotein are coupled to a protein stain, and staining the protein associated with the lipoproteins by reacting the protein stain coupled antibodies with the sample.

The method of claim A, wherein the antibody molecules bind a apolipoproteins present in the lipoproteins and the apolipoproteins are selected from the group consisting of ApoA-I, ApoA-II, Apo B, Apo C-III and Apo E.

The method of claim A, wherein the biological sample is selected from the group consisting of blood, plasma and serum.

Status of Claims

14. Claims 46 and 47 are allowed. All other claims stand rejected.

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Sunday-Thursday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
December 3, 2001

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600